ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ARICLAIM 40 mg hard gastro-resistant capsules.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 40 mg of duloxetine (as hydrochloride).

Excipients: sucrose 11.5 mg .
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard gastro-resistant capsule.

Opaque orange body, imprinted with ’40mg’ and an opaque blue cap, imprinted with ‘9545’.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ARICLAIM is indicated for women for the treatment of moderate to severe Stress Urinary Incontinence (SUI), (see section 5.1).
Treatment of diabetic peripheral neuropathic pain in adults.

4.2 Posology and method of administration

Stress Urinary Incontinence:
The recommended dose of ARICLAIM is 40 mg twice daily without regard to meals. After 2-4 weeks of treatment, patients should be re-assessed in order to evaluate the benefit and tolerability of the therapy. Some patients may benefit from starting treatment at a dose of 20 mg twice daily for two weeks before increasing to the recommended dose of 40 mg twice daily. Dose escalation may decrease, though not eliminate, the risk of nausea and dizziness.
However, limited data are available to support the efficacy of ARICLAIM 20 mg twice daily.
A 20 mg capsule is also available.

The efficacy of ARICLAIM has not been evaluated for longer than 3 months in placebo-controlled studies. The benefit of treatment should be re-assessed at regular intervals.

Combining ARICLAIM with a pelvic floor muscle training (PFMT) program may be more effective than either treatment alone. It is recommended that consideration be given to concomitant PFMT.

Diabetic Peripheral Neuropathic Pain:
The starting and recommended maintenance dose is 60 mg daily with or without food. Dosages above 60 mg once daily, up to a maximum dose of 120 mg per day administered in evenly divided doses, have been evaluated from a safety perspective in clinical trials. The plasma concentration of duloxetine displays large inter-individual variability (see 5.2). Hence, some patients that respond insufficiently to 60 mg may benefit from a higher dose.

The medicinal product response should be evaluated after 2 months’ of treatment. Additional response after this time is unlikely (see 5.1).

The therapeutic benefit should regularly (at least every three months) be reassessed.

Hepatic insufficiency:
ARICLAIM should not be used in patients with liver disease resulting in hepatic impairment (see section 4.3).

Renal insufficiency:
No dosage adjustment is necessary for patients with mild or moderate renal dysfunction (creatinine clearance 30 to 80 ml/min). ARICLAIM should not be used in patients with severe renal impairment (creatinine clearance <30 ml/min; see section 4.3).

Elderly
No dosage adjustment is recommended for elderly patients solely on the basis of age. Caution should be exercised when treating the elderly

Children and adolescents:
There is no experience in children (see section 4.4).
Discontinuation of treatment:
Abrupt discontinuation should be avoided. When stopping treatment with ARICLAIM the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions (see sections 4.4 and 4.8). If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Liver disease resulting in hepatic impairment (see section 5.2).

Pregnancy and lactation (see section 4.6).

ARICLAIM should not be used in combination with nonselective, irreversible Monoamine Oxidase Inhibitors - MAOIs (see section 4.5).

ARICLAIM should not be used in combination with CYP1A2 inhibitors, like fluvoxamine, ciprofloxacin or enoxacine since the combination results in elevated plasma concentrations of duloxetine (see section 4.5).

Severe renal impairment (creatinine clearance <30 ml/min) (see section 4.4).

The initiation of treatment with ARICLAIM is contraindicated in patients with uncontrolled hypertension that could expose patients to a potential risk of hypertensive crisis (see sections 4.4 and 4.8).

4.4 Special warnings and precautions for use

Mania and Seizures
ARICLAIM should be used with caution in patients with a history of mania or a diagnosis of bipolar disorder, and/or seizures.

Use with antidepressants
The use of ARICLAIM in combination with antidepressants (especially with SSRI, SNRI and reversible MAOIs) is not recommended (see below “Depression, suicidal ideation and behaviour” and Section 4.5).

St John’s wort
Undesirable effects may be more common during concomitant use of ARICLAIM and herbal preparations containing St John’s wort (Hypericum perforatum).

Mydriasis
Mydriasis has been reported in association with duloxetine, therefore, caution should be used when prescribing duloxetine in patients with increased intraocular pressure, or those at risk of acute narrow-angle glaucoma.

Blood pressure and heart rate
Duloxetine has been associated with an increase in blood pressure and clinically significant hypertension in some patients. This may be due to the noradrenergic effect of duloxetine. Cases of hypertensive crisis have been reported with duloxetine, especially in patients with pre-existing hypertension. Therefore,in patients with known hypertension and/or other cardiac disease, blood pressure monitoring is recommended, especially during the first month of treatment. Duloxetine should be used with caution in patients whose conditions could be compromised by an increased heart rate or by an increase in blood pressure. Caution should also be exercised when duloxetine is used with medicinal products that may impair its metabolism (see section 4.5). For patients who experience a sustained increase in blood pressure while receiving duloxetine either dose reduction or gradual discontinuation should be considered (see section 4.8). In patients with uncontrolled hypertension duloxetine should not be initiated (see section 4.3).

Renal impairment
Increased plasma concentrations of duloxetine occur in patients with severe renal impairment on haemodialysis (creatinine clearance <30 ml/min). For patients with severe renal impairment, see section 4.3. See section 4.2 for information on patients with mild or moderate renal dysfunction.

Haemorrhage
There have been reports of bleeding abnormalities, such as ecchymoses, purpura and gastrointestinal haemorrhage with selective serotonin reuptake inhibitors (SSRIs) and serotonin/norepinephrine reuptake inhibitors (SNRIs). Caution is advised in patients taking anticoagulants and/or medicinal products known to affect platelet function, and in patients with known bleeding tendencies.

Discontinuation of treatment
Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8). In a clinical trial adverse events seen on abrupt treatment discontinuation occurred in approximately 44% of patients treated with ARICLAIM and 24% of patients taking placebo.
The risk of withdrawal symptoms seen with SSRI's and SNRI's may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction. The most commonly reported reactions are listed in section 4.8. Generally the symptoms are mild to moderate, however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that duloxetine should be gradually tapered when discontinuing treatment over a period of no less than 2 weeks, according to the patient's needs (see section 4.2).

Hyponatremia
Hyponatremia has been reported rarely, predominantly in the elderly, when administering ARICLAIM. Caution is required in patients at increased risk for hyponatremia; such as elderly, cirrhotic, or dehydrated patients or patients treated with diuretics. Hyponatremia may be due to a syndrome of inappropriate anti-diuretic hormone secretion (SIADH).

Depression, suicidal ideation and behaviour
Although ARICLAIM is not indicated for the treatment of depression, its active ingredient (duloxetine) also exists as an antidepressant medication. Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical

experience that the risk of suicide may increase in the early stages of recovery. Patients with a history of suicide-related events or those exhibiting a significant degree of suicidal thoughts prior to commencement of treatment are known to be at a greater risk of suicidal thoughts or suicidal behaviour, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant medicinal products in psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old
Cases of suicidal thoughts and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation (see section 4.8). Physicians should encourage patients to report any distressing thoughts or feelings or depressive symptoms at any time. If while on ARICLAIM therapy, the patient develops agitation or depressive symptoms, specialised medical advice should be sought, as depression is a serious medical condition. If a decision to initiate antidepressant pharmacological therapy is taken, the gradual discontinuation of ARICLAIM is recommended (see Section 4.2).

Use in children and adolescents under 18 years of age
No clinical trials have been conducted with duloxetine in paediatric populations. ARICLAIM should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempts and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger), were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. Long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Medicinal products containing duloxetine
Duloxetine is used under different trademarks in several indications (treatment of diabetic neuropathic pain, major depressive episodes as well as stress urinary incontinence). The use of more than one of these products concomitantly should be avoided.

Hepatitis/increased liver enzymes
Cases of liver injury, including severe elevations of liver enzymes (>10 times upper limit of normal), hepatitis and jaundice have been reported with duloxetine (see section 4.8). Most of them occurred during the first months of treatment. The pattern of liver damage was predominantly hepatocellular. Duloxetine should be used with caution in patients treated with other medicinal products associated with hepatic injury.

Akathisia/psychomotor restlessness
The use of duloxetine has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Sucrose
ARICLAIM gastro-resistant capsules contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Monoamine oxidase inhibitors (MAOIs): due to the risk of serotonin syndrome, ARICLAIM should not be used in combination with nonselective, irreversible monoamine oxidase inhibitors (MAOIs), or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of duloxetine, at least 5 days should be allowed after stopping ARICLAIM before starting an MAOI (see section 4.3).

Serotonin syndrome: in rare cases, serotonin syndrome has been reported in patients using SSRIs (e.g. paroxetine, fluoxetine) concomitantly with serotonergic medicinal products. Caution is advisable if

ARICLAIM is used concomitantly with serotonergic antidepressants like SSRIs, tricyclics like clomipramine or amitriptyline, St John's wort (Hypericum perforatum), venlafaxine or triptans, tramadol, pethidine and tryptophan.

CNS medicinal products: caution is advised when ARICLAIM is taken in combination with other centrally acting medicinal products or substances, including alcohol and sedative medicinal products (benzodiazepines, morphinomimetics, antipsychotics, phenobarbital, sedative antihistamines).

Effect of duloxetine on other medicinal products
Medicinal products metabolised by CYP1A2: The pharmacokinetics of theophylline, a CYP1A2 substrate, were not significantly affected by co-administration with duloxetine (60 mg twice daily).
Medicinal products metabolised by CYP2D6: Duloxetine is a moderate inhibitor of CYP2D6. When duloxetine was administered at a dose of 60 mg twice daily with a single dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold. The co-administration of duloxetine (40 mg twice daily) increases steady state AUC of tolterodine (2 mg twice daily) by 71 %, but does not affect the pharmacokinetics of its active 5-hydroxyl metabolite and no dosage adjustment is recommended. Caution is advised if ARICLAIM is co-administered with medicinal products that are predominantly metabolised by CYP2D6 (risperidone, tricyclic antidepressants [TCAs] such as nortriptyline, amitriptyline, and imipramine) particularly if they have a narrow therapeutic index (such as flecainide, propafenone and metoprolol).

Oral contraceptives and other steroidal agents: results of *in vitro* studies demonstrate that duloxetine does not induce the catalytic activity of CYP3A. Specific *in vivo* drug interaction studies have not been performed.

Anticoagulants and antiplatelet agents: Caution should be exercised when duloxetine is combined with oral anticoagulants or antiplatelet agents due to a potential increased risk of bleeding. Furthermore, increases in INR values have been reported when duloxetine was co-administered with warfarin.

Effects of other medicinal products on duloxetine
Antacids and H2 antagonists: co-administration of ARICLAIM with aluminium- and magnesium-containing antacids or with famotidine had no significant effect on the rate or extent of duloxetine absorption after administration of a 40 mg oral dose.

Inhibitors of CYP1A2: because CYP1A2 is involved in duloxetine metabolism, concomitant use of ARICLAIM with potent inhibitors of CYP1A2 is likely to result in higher concentrations of duloxetine. Fluvoxamine (100 mg once daily), a potent inhibitor of CYP1A2, decreased the apparent plasma clearance of duloxetine by about 77% and increased $AUC_{0\text{-}t}$ 6-fold. Therefore ARICLAIM should not be administered in combination with potent inhibitors of CYP1A2 like fluvoxamine (see section 4.3).

Inducers of CYP1A2: Population pharmacokinetic studies analyses have shown that smokers have almost 50% lower plasma concentrations of duloxetine compared with non-smokers.

4.6 Pregnancy and lactation

Pregnancy
There are no data on the use of duloxetine in pregnant women. Studies in animals have shown reproductive toxicity at systemic exposure levels (AUC) of duloxetine lower than the maximum clinical exposure (see section 5.3). The potential risk for humans is unknown. Withdrawal symptoms may occur in the neonate after maternal duloxetine use near term. ARICLAIM is contraindicated during pregnancy (see section 4.3).

Breast feeding
Duloxetine is very weakly excreted into human milk based on a study of 6 lactating patients, who did not breast feed their children . The estimated daily infant dose on a mg/kg basis is approximately

0.14% of the maternal dose (see section 5.2). As the safety of duloxetine in infants is not known, the use of ARICLAIM while breast-feeding is not recommended.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. ARICLAIM may be associated with sedation and dizziness. Patients should be instructed that if they experience sedation or dizziness they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects

Stress Urinary Incontinence:

Table 1 gives the adverse reactions observed from spontaneous reporting and in placebo-controlled clinical trials (comprising a total of 7977 patients, 4371 on duloxetine and 3606 on placebo) in SUI and other lower urinary tract disorders.
The most commonly reported adverse events in patients treated with ARICLAIM in clinical trials in SUI and other lower urinary tract disorders were nausea, dry mouthand fatigue -. The data analysis of four 12-week, placebo-controlled clinical trials in patients with SUI, including 958 duloxetine-treated and 955 placebo-treated patients, showed that the onset of the reported adverse events typically occurred in the first week of therapy. However, the majority of the most frequent adverse events were mild to moderate and resolved within 30 days of occurrence (e.g. nausea).

Table 1: Adverse reactions
Frequency estimate: Very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1,000 and <1/100), rare (≥ 1/10,000 and <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Very common	Common	Uncommon	Rare	Very Rare	Frequency not known
Investigations					
		Weight increase Weight decrease Creatinine phosphokinase increase Blood cholesterol increased			
Cardiac Disorders					
	Palpitations	Tachycardia			Supra-ventricular arrhythmia, mainly atrial fibrillation
Nervous System Disorders					
	Headache Dizziness Tremor Nervousness Lethargy Somnolence	Dysgeusia Disturbance in attention	Myoclonus Dyskinesia		Serotonin syndrome Extrapyramidal symptoms Convulsions Akathisia

	Paraesthesia				Psychomotor restlessness
Eye Disorders					
	Blurred vision	Mydriasis Visual disturbance	Glaucoma		
Ear and Labyrinth Disorders					
	Vertigo	Ear pain			
Respiratory, thoracic and mediastinal disorders					
		Yawning	Throat tightness Epistaxis		
Gastrointestinal Disorders					
Nausea (22%) Dry mouth (11.2%)	Constipation Diarrhoea Vomiting Dyspepsia	Eructation Gastroenteritis Stomatitis Halitosis Gastritis Flatulence	Haematochezia		Gastrointestinal haemorrhage
Renals and Urinary Disorders					
		Nocturia Urinary hesitation Urine odour abnormal Dysuria			Urinary retention
Skin and Subcutaneous Tissue Disorders					
	Sweating increased	Night sweats Cold sweat Rash Increased tendency to bruise	Photo-sensitivity reactions		Angioneurotic oedema Stevens-Johnson Syndrome Urticaria
Muscoskeletal and connective tissue disorders					
		Muscle tightness Musculo-skeletal pain Trismus Muscle spasm	Muscle twitching		
Endocrine disorders					
		Hypo-thyroidism			
Metabolism and Nutrition Disorders					
	Appetite decreased	Dehydration	Hyperglycemia (reported especially in diabetic patients)		Hyponatremia, SIADH
Infections and infestations					
		Laryngitis			
Vascular Disorders					
	Hot flush	Flushing Blood pressure	Peripheral coldness		Hypertension

		increase Syncope[1]	Orthostatic hypotension[1] Hypertensive crisis		
General Disorders and Administration Site Conditions					
Fatigue (10.3%)	Pruritus Weakness Abdominal pain Chills	Feeling hot Malaise Thirst Feeling abnormal	Feeling cold		Chest pain
Immune system disorders					
		Hyper-sensitivity disorder			Anaphylactic reaction
Hepato-biliary disorders					
		Elevated liver enzymes (ALT, AST, alkaline phosphatase) Hepatitis[2] Acute liver injury			Jaundice Hepatic failure
Reproductive System and Breast Disorders					
		Menopausal symptoms Gynaecological haemorrhage			
Psychiatric Disorders					
	Insomnia Sleep disorder Anxiety Libido decreased Agitation	Bruxism Disorientation Orgasm abnormal Apathy Abnormal dreams			Hallucinations Mania

[1]Cases of orthostatic hypotension and syncope have been reported especially at the initiation of treatment
[2]See section 4.4

Discontinuation of duloxetine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, headache, irritability, diarrhoea, hyperhydrosis and vertigo are the most commonly reported reactions.
Generally, for SSRIs and SNRIs, these events are mild to moderate and self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when duloxetine treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 4.2 and 4.4).

Electrocardiograms were obtained from 755 duloxetine-treated patients with SUI and 779 placebo-treated patients in 12-week clinical trials. The heart rate-corrected QT interval in duloxetine-treated patients did not differ from that seen in placebo-treated patients.

In the 12 week acute phase of three clinical trials of duloxetine in patients with diabetic neuropathic pain, small but statistically significant increases in fasting blood glucose were observed in duloxetine-

treated patients . HbA_{1c} was stable in both duloxetine-treated and placebo-treated patients. In the extension phase of these studies, which lasted up to 52 weeks, there was an increase in HbA_{1c} in both the duloxetine and routine care groups, but the mean increase was 0.3% greater in the duloxetine-treated group. There was also a small increase in fasting blood glucose and in total cholesterol in duloxetine-treated patients while those laboratory tests showed a slight decrease in the routine care group.

Diabetic Peripheral Neuropathic Pain
Table 2 gives the adverse reactions observed from spontaneous reporting and in placebo-controlled clinical trials (comprising a total of 4926 patients, 3127 on duloxetine and 1799 on placebo).
The most commonly observed adverse reactions in patients with diabetic neuropathic pain treated with ARICLAIM were: nausea; somnolence; headache and dizziness.

Table 2: Adverse reactions
Frequency estimate: Very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1,000 and <1/100), rare (≥ 1/10,000 and <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Very common	**Common**	**Uncommon**	**Rare**	**Very Rare**	**Frequency not known**
Investigations					
	Weight decrease	Weight increase Creatinine phosphokinase increase	Blood cholesterol increased		
Cardiac Disorders					
	Palpitations	Tachycardia			Supra-ventricular arrhythmia, mainly atrial fibrillation
Nervous System Disorders					
Headache (14.2%)Somnolence (11.1%)	Dizziness Tremor Nervousness Lethargy Paraesthesia	Dysgeusia Disturbance in attention Myoclonus Dyskinesia			Serotonin syndrome Extra-pyramidal symptoms Convulsions Akathisia Psychomotor restlessness
Eye Disorders					
	Blurred vision	Mydriasis Visual disturbance	Glaucoma		
Ear and Labyrinth Disorders					
		Vertigo Ear pain			
Respiratory, thoracic and mediastinal disorders					
	Yawning	Throat tightness Epistaxis			

Gastrointestinal Disorders					
Nausea (21.7%) Dry mouth (13.4%) Diarrhoea (10.2%)	Constipation Vomiting Dyspepsia Flatulence	Eructation Gastroenteritis Stomatitis Gastritis	Halitosis Haematochezia		Gastrointestinal haemorrhage
Renals and Urinary Disorders					
		Nocturia Urinary hesitation Urinary Retention Dysuria			Urine odour abnormal
Skin and Subcutaneous Tissue Disorders					
	Sweating increased Rash	Night sweats Photo-sensitivity reactions Cold sweat Increased tendency to bruise			Angio-neurotic oedema Stevens-Johnson Syndrome Urticaria
Muscoskeletal and connective tissue disorders					
	Musculo-skeletal pain Muscle tightness Muscle spasm	Muscle twitching	Trismus		
Endocrine disorders					
			Hypo-thyroidism		
Metabolism and Nutrition Disorders					
	Decreased Appetite	Hyperglycemia (reported especially in diabetic patients)	Dehydration		Hypo-natremia SIADH
Infections and infestations					
		Laryngitis			
Vascular Disorders					
	Hot flush	Flushing Blood pressure increase Peripheral coldness Orthostatic hypotension[1] Syncope[1]			Hypertension Hypertensive crisis
General Disorders and Administration Site Conditions					
	Fatigue Abdominal pain	Feeling hot Feeling cold Malaise Thirst Feeling			Chest pain

		abnormal Chills			
Immune system disorders					
		Hyper-sensitivity disorder			Anaphylactic reaction
Hepato-biliary disorders					
		Elevated liver enzymes (ALT, AST, alkaline phosphatase) Hepatitis[2] Acute liver injury			Jaundice Hepatic failure
Reproductive System and Breast Disorders					
	Erectile dysfunction	Ejaculation disorder Ejaculation delayed Gynaecological haemorrhage	Menopausal symptoms		
Psychiatric Disorders					
Insomnia (10.2%)	Anxiety Libido decreased Orgasm abnormal Agitation Abnormal dreams	Bruxism Disorientation Sleep disorder Apathy	Mania		Suicidal ideation[3] Suicidal behaviour[3] Hallucinations

[1] Cases of orthostatic hypotension and syncope have been reported especially at the initiation of treatment.
[2] See section 4.4.
[3] Cases of suicidal ideation and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation (see section 4.4).

Discontinuation of duloxetine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, headache, irritability, diarrhoea, hyperhydrosis and vertigo are the most commonly reported reactions.
Generally, for SSRIs and SNRIs, these events are mild to moderate and self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when duloxetine treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 4.2 and 4.4).

In the 12 week acute phase of three clinical trials of duloxetine in patients with diabetic neuropathic pain, small but statistically significant increases in fasting blood glucose were observed in duloxetine-treated patients. HbA1c was stable in both duloxetine-treated and placebo-treated patients. In the extension phase of these studies, which lasted up to 52 weeks, there was an increase in HbA1c in both the duloxetine and routine care groups, but the mean increase was 0.3% greater in the duloxetine-treated group. There was also a small increase in fasting blood glucose and in total cholesterol in duloxetine-treated patients while those laboratory tests showed a slight decrease in the routine care group.

Electrocardiograms were obtained from 528 duloxetine-treated and 205 placebo-treated patients with diabetic neuropathic pain in clinical trials lasting up to 13-weeks. The heart rate-corrected QT interval in duloxetine-treated patients did not differ from that seen in placebo-treated patients. No clinically significant differences were observed for QT, PR, QRS, or QTcB measurements between duloxetine-treated and placebo-treated patients.

4.9 Overdose

There is limited clinical experience with duloxetine overdose in humans. Cases of overdoses, alone or in combination with other medicinal products, with duloxetine doses of 4800mg were reported. Some fatalities have occurred, primarily with mixed overdoses, but also with duloxetine alone at a dose of approximately 1000 mg. Signs and symptoms of overdose (mostly with mixed medicinal products) included serotonin syndrome, somnolence, vomiting and seizures.

No specific antidote for duloxetine is known but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered.. A free airway should be established. Monitoring of cardiac and vital signs is recommended, along with appropriate symptomatic and supportive measures. Gastric lavage may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal may be useful in limiting absorption. Duloxetine has a large volume of distribution and forced diuresis, haemoperfusion, and exchange perfusion are unlikely to be beneficial.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antidepressants. ATC code: N06AX21

Duloxetine is a combined serotonin (5-HT) and norepinephrine (NE) reuptake inhibitor. It weakly inhibits dopamine reuptake with no significant affinity for histaminergic, dopaminergic, cholinergic and adrenergic receptors.

In animal studies, increased levels of 5-HT and NE in the sacral spinal cord, lead to increased urethral tone via enhanced pudendal nerve stimulation to the urethral striated sphincter muscle only during the storage phase of the micturition cycle. A similar mechanism in women is believed to result in stronger urethral closure during urine storage with physical stress that could explain the efficacy of duloxetine in the treatment of women with SUI.

Duloxetine normalised pain thresholds in several preclinical models of neuropathic and inflammatory pain and attenuated pain behaviour in a model of persistent pain. The pain inhibitory action of duloxetine is believed to be a result of potentiation of descending inhibitory pain pathways within the central nervous system.

Stress Urinary Incontinence: The efficacy of duloxetine 40 mg given twice daily in the treatment of SUI was established in four double-blind, placebo-controlled studies, that randomised 1913 women (22 to 83 years) with SUI; of these, 958 patients were randomised to duloxetine and 955 to placebo. The primary efficacy measures were Incontinence Episode Frequency (IEF) from diaries and an incontinence specific quality of life questionnaire score (I-QOL).

Incontinence Episode Frequency: in all four studies the duloxetine-treated group had a 50% or greater median decrease in IEF compared with 33% in the placebo-treated group. Differences were observed at each visit after 4 weeks (duloxetine 54%, and placebo 22%), 8 weeks (52% and 29%), and 12 weeks (52% and 33%) of medication.

In an additional study limited to patients with severe SUI, all responses with duloxetine were achieved within 2 weeks.

The efficacy of ARICLAIM has not been evaluated for longer than 3 months in placebo-controlled studies. The clinical benefit of ARICLAIM compared with placebo has not been demonstrated in women with mild SUI, defined in randomised trials as those with IEF < 14 per week. In these women, ARICLAIM may provide no benefit beyond that afforded by more conservative behavioural interventions.

Quality of Life: Incontinence Quality of Life (I-QOL) questionnaire scores were significantly improved in the duloxetine-treated patient group compared with the placebo-treated group (9.2 versus 5.9 score improvement, p<.001). Using a global improvement scale (PGI), significantly more women using duloxetine considered their symptoms of stress incontinence to be improved with treatment compared with women using placebo (64.6% versus 50.1%, p<.001).

ARICLAIM and Prior Continence Surgery: there are limited data that suggest that the benefits of ARICLAIM are not diminished in women with stress urinary incontinence who have previously undergone continence surgery.

ARICLAIM and Pelvic Floor Muscle Training (PFMT): during a 12-week blinded, randomised, controlled study, ARICLAIM demonstrated greater reductions in IEF compared with either placebo treatment or with PFMT alone. Combined therapy (duloxetine + PFMT) showed greater improvement in both pad use and condition-specific quality of life measures than ARICLAIM alone or PFMT alone.

Diabetic Peripheral Neuropathic Pain:
The efficacy of duloxetine as a treatment for diabetic neuropathic pain was established in 2 randomised, 12-week, double-blind, placebo-controlled, fixed dose studies in adults (22 to 88 years) having diabetic neuropathic pain for at least 6 months. Patients meeting diagnostic criteria for major depressive disorder were excluded from these trials. The primary outcome measure was the weekly mean of 24-hour average pain, which was collected in a daily diary by patients on an 11-point Likert scale.

In both studies, duloxetine 60 mg once daily and 60 mg twice daily significantly reduced pain compared with placebo. The effect in some patients was apparent in the first week of treatment. The difference in mean improvement between the two active treatment arms was not significant. At least 30% reported pain reduction was recorded in approximately 65% of duloxetine treated patients versus 40% for placebo. The corresponding figures for at least 50% pain reduction were 50% and 26% respectively. Clinical response rates (50% or greater improvement in pain) were analysed according to whether or not the patient experienced somnolence during treatment. For patients not experiencing somnolence, clinical response was observed in 47% of patients receiving duloxetine and 27% patients on placebo. Clinical response rates in patients experiencing somnolence were 60% on duloxetine and 30% on placebo. Patients not demonstrating a pain reduction of 30% within 60 days of treatment were unlikely to reach this level during further treatment.

Although data from a one-year open label study offer some evidence for longer-term efficacy, no conclusive efficacy data for treatments longer than 12 weeks duration are available from placebo-controlled studies.

5.2 Pharmacokinetic properties

Duloxetine is administered as a single enantiomer. Duloxetine is extensively metabolised by oxidative enzymes (CYP1A2 and the polymorphic CYP2D6), followed by conjugation. The pharmacokinetics of duloxetine demonstrate large intersubject variability (generally 50-60%), partly due to gender, age, smoking status and CYP2D6 metaboliser status.

Duloxetine is well absorbed after oral administration with a C_{max} occurring 6 hours post dose. The absolute oral bioavailability of duloxetine ranged from 32% to 80% (mean of 50%; N=8 subjects).

Food delays the time to reach the peak concentration from 6 to 10 hours and it marginally decreases the extent of absorption (approximately 11%).

Duloxetine is approximately 96% bound to human plasma proteins. Duloxetine binds to both albumin and alpha-1 acid glycoprotein. Protein binding is not affected by renal or hepatic impairment.

Duloxetine is extensively metabolised and the metabolites are excreted principally in urine. Both CYP2D6 and CYP1A2 catalyse the formation of the two major metabolites glucuronide conjugate of 4-hydroxy duloxetine and sulphate conjugate of 5-hydroxy,6-methoxy duloxetine. Based upon *in vitro* studies, the circulating metabolites of duloxetine are considered pharmacologically inactive. The pharmacokinetics of duloxetine in patients who are poor metabolisers with respect to CYP2D6 has not been specifically investigated. Limited data suggest that the plasma levels of duloxetine are higher in these patients.

The elimination half-life of duloxetine after an oral dose ranges from 8 to 17 hours (mean of 12 hours). After an intravenous dose the plasma clearance of duloxetine ranges from 22 l/hr to 46 l/hr (mean of 36 l/hr) After an oral dose the apparent plasma clearance of duloxetine ranges from 33 to 261 l/hr (mean 101 l/hr).

Special populations:
Gender: pharmacokinetic differences have been identified between males and females (apparent plasma clearance is approximatively 50% lower in females). Based upon the overlap in the range of clearance, gender-based pharmacokinetic differences do not justify the recommendation for using a lower dose for female patients.

Age: pharmacokinetic differences have been identified between younger and elderly females (≥65 years) (AUC increases by about 25% and half-life is about 25% longer in the elderly), although the magnitude of these changes is not sufficient to justify adjustments to the dose. As a general recommendation, caution should be exercised when treating the elderly (see sections 4.2 and 4.4).

Renal impairment: end stage renal disease (ESRD) patients receiving dialysis had a 2-fold higher duloxetine C_{max} and AUC values compared to healthy subjects. Pharmacokinetic data on duloxetine is limited in patients with mild or moderate renal impairment.

Hepatic insufficiency: moderate liver disease (Child Pugh Class B) affected the pharmacokinetics of duloxetine. Compared with healthy subjects, the apparent plasma clearance of duloxetine was 79% lower, the apparent terminal half-life was 2.3 times longer, and the AUC was 3.7 times higher in patients with moderate liver disease. The pharmacokinetics of duloxetine and its metabolites have not been studied in patients with mild or severe hepatic insufficiency.

Nursing mothers: The disposition of duloxetine was studied in 6 lactating women who were at least 12-weeks postpartum. Duloxetine is detected in breast milk, and steady-state concentrations in breast milk are about one-fourth those in plasma. The amount of duloxetine in breast milk is approximately 7 μg/day while on 40 mg twice daily dosing. Lactation did not influence duloxetine pharmacokinetics.

5.3 Preclinical safety data

Duloxetine was not genotoxic in a standard battery of tests and was not carcinogenic in rats. Multinucleated cells were seen in the liver in the absence of other histopathological changes in the rat carcinogenicity study. The underlying mechanism and the clinical relevance are unknown.

Female mice receiving duloxetine for 2 years had an increased incidence of hepatocellular adenomas and carcinomas at the high dose only (144 mg/kg/day), but these were considered to be secondary to hepatic microsomal enzyme induction. The relevance of this mouse data to humans is unknown. Female rats receiving duloxetine before and during mating and early pregnancy had a decrease in maternal food consumption and body weight, oestrous cycle disruption, decreased live birth indices and progeny survival, and progeny growth retardation at systemic exposure levels estimated to be at

the most at maximum clinical exposure (AUC). In an embryotoxicity study in the rabbit, a higher incidence of cardiovascular and skeletal malformations was observed at systemic exposure levels below the maximun clinical exposure (AUC). No malformations were observed in another study testing a higher dose of a different salt of duloxetine. In pre/postnatal toxicity study in the rat, duloxetine induced adverse behavioural effects in the offspring at systemic exposures levels below maximum clinical exposure (AUC).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Hypromellose.
Hydroxypropyl methylcellulose acetate succinate
Sucrose
Sugar spheres
Talc
Titanium dioxide (E171)
Triethyl citrate.

Capsule shell:
Gelatin
Sodium Lauryl Sulfate
Titanium Dioxide (E171)
Indigo Carmine (E132)
Red Iron oxide (E172)
Yellow Iron Oxide (E172)
Edible black ink.

Edible Ink:
Black Iron Oxide-Synthetic (E172)
Propylene glycol
Shellac.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture. Do not store above 30°C.

6.5 Nature and contents of container

Polyvinylchloride (PVC), Polyethylene (PE), and Polychlorotrifluoroethylene (PCTFE) blister sealed with an aluminum foil.

Packs of 28, 56, 98, 140 and 196 (2x98) capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland BV, Grootslag 1-5, NL-3991 RA Houten, The Netherlands.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/283/002
EU/1/04/283/003
EU/1/04/283/004
EU/1/04/283/005
EU/1/04/283/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11 August 2004

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

ARICLAIM 20 mg hard gastro-resistant capsules.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 20 mg of duloxetine (as hydrochloride).

Excipients: sucrose 5.7 mg.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard gastro-resistant capsule.

Opaque blue body, imprinted with '20 mg' and an opaque blue cap, imprinted with '9544'.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ARICLAIM is indicated for women for the treatment of moderate to severe Stress Urinary Incontinence (SUI), (see section 5.1).
Treatment of diabetic peripheral neuropathic pain in adults.

4.2 Posology and method of administration

Stress Urinary Incontinence:
The recommended dose of ARICLAIM is 40 mg twice daily without regard to meals. After 2-4 weeks of treatment, patients should be re-assessed in order to evaluate the benefit and tolerability of the therapy. Some patients may benefit from starting treatment at a dose of 20 mg twice daily for two weeks before increasing to the recommended dose of 40 mg twice daily. Dose escalation may decrease, though not eliminate, the risk of nausea and dizziness.
However, limited data are available to support the efficacy of ARICLAIM 20 mg twice daily.

The efficacy of ARICLAIM has not been evaluated for longer than 3 months in placebo-controlled studies. The benefit of treatment should be re-assessed at regular intervals.

Combining ARICLAIM with a pelvic floor muscle training (PFMT) program may be more effective than either treatment alone. It is recommended that consideration be given to concomitant PFMT.

Diabetic Peripheral Neuropathic Pain:
The starting and recommended maintenance dose is 60 mg daily with or without food. Dosages above 60 mg once daily, up to a maximum dose of 120 mg per day administered in evenly divided doses, have been evaluated from a safety perspective in clinical trials. The plasma concentration of duloxetine displays large inter-individual variability (see 5.2). Hence, some patients that respond insufficiently to 60 mg may benefit from a higher dose.

The medicinal product response should be evaluated after 2 months' of treatment. Additional response after this time is unlikely (see 5.1).

The therapeutic benefit should regularly (at least every three months) be reassessed.

Hepatic insufficiency:
ARICLAIM should not be used in patients with liver disease resulting in hepatic impairment (see section 4.3).

Renal insufficiency:
No dosage adjustment is necessary for patients with mild or moderate renal dysfunction (creatinine clearance 30 to 80 ml/min). ARICLAIM should not be used in patients with severe renal impairment (creatinine clearance <30 ml/min; see section 4.3).

Elderly:
No dosage adjustment is recommended for elderly patients solely on the basis of age. Caution should be exercised when treating the elderly.

Children and adolescents:
There is no experience in children (see section 4.4).
Discontinuation of treatment:
Abrupt discontinuation should be avoided. When stopping treatment with ARICLAIM the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions (see sections 4.4 and 4.8). If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Liver disease resulting in hepatic impairment (see section 5.2).

Pregnancy and lactation (see section 4.6).

ARICLAIM should not be used in combination with nonselective, irreversible Monoamine Oxidase Inhibitors - MAOIs (see section 4.5).

ARICLAIM should not be used in combination with CYP1A2 inhibitors, like fluvoxamine, ciprofloxacin or enoxacine since the combination results in elevated plasma concentrations of duloxetine (see section 4.5).

Severe renal impairment (creatinine clearance <30 ml/min) (see section 4.4).

The initiation of treatment with ARICLAIM is contraindicated in patients with uncontrolled hypertension that could expose patients to a potential risk of hypertensive crisis (see sections 4.4 and 4.8).

4.4 Special warnings and precautions for use

Mania and Seizures
ARICLAIM should be used with caution in patients with a history of mania or a diagnosis of bipolar disorder, and/or seizures.

Use with antidepressants
The use of ARICLAIM in combination with antidepressants (especially with SSRI, SNRI and reversible MAOIs) is not recommended (see below “Depression, suicidal ideation and behaviour” and Section 4.5).

St John's wort
Undesirable effects may be more common during concomitant use of ARICLAIM and herbal preparations containing St John's wort (Hypericum perforatum).

Mydriasis
Mydriasis has been reported in association with duloxetine, therefore, caution should be used when prescribing duloxetine in patients with increased intraocular pressure, or those at risk of acute narrow-angle glaucoma.

Blood pressure and heart rate
Duloxetine has been associated with an increase in blood pressure and clinically significant hypertension in some patients. This may be due to the noradrenergic effect of duloxetine. Cases of hypertensive crisis have been reported with duloxetine, especially in patients with pre-existing hypertension. Therefore,in patients with known hypertension and/or other cardiac disease, blood pressure monitoring is recommended, especially during the first month of treatment. Duloxetine should be used with caution in patients whose conditions could be compromised by an increased heart rate or by an increase in blood pressure. Caution should also be exercised when duloxetine is used with medicinal products that may impair its metabolism (see section 4.5). For patients who experience a sustained increase in blood pressure while receiving duloxetine either dose reduction or gradual discontinuation should be considered (see section 4.8). In patients with uncontrolled hypertension duloxetine should not be initiated (see section 4.3).

Renal impairment
Increased plasma concentrations of duloxetine occur in patients with severe renal impairment on haemodialysis (creatinine clearance <30 ml/min). For patients with severe renal impairment, see section 4.3. See section 4.2 for information on patients with mild or moderate renal dysfunction.
Haemorrhage
There have been reports of bleeding abnormalities, such as ecchymoses, purpura and gastrointestinal haemorrhage with selective serotonin reuptake inhibitors (SSRIs) and serotonin/norepinephrine reuptake inhibitors (SNRIs). Caution is advised in patients taking anticoagulants and/or medicinal products known to affect platelet function, and in patients with known bleeding tendencies.

Discontinuation of treatment
Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8). In a clinical trial, adverse events seen on abrupt treatment discontinuation occurred in approximately 44% of patients treated with ARICLAIM and 24% of patients taking placebo.
The risk of withdrawal symptoms seen with SSRI's and SNRI's may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction. The most commonly reported reactions are listed in section 4.8. Generally the symptoms are mild to moderate, however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that duloxetine should be gradually tapered when discontinuing treatment over a period of no less than 2 weeks, according to the patient's needs (see section 4.2).

Hyponatremia
Hyponatremia has been reported rarely, predominantly in the elderly, when administering ARICLAIM. Caution is required in patients at increased risk for hyponatremia; such as elderly, cirrhotic, or dehydrated patients or patients treated with diuretics. Hyponatremia may be due to a syndrome of inappropriate anti-diuretic hormone secretion (SIADH).

Depression, suicidal ideation and behaviour
Although ARICLAIM is not indicated for the treatment of depression, its active ingredient (duloxetine) also exists as an antidepressant medication. Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until

significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery. Patients with a history of suicide-related events or those exhibiting a significant degree of suicidal thoughts prior to commencement of treatment are known to be at a greater risk of suicidal thoughts or suicidal behaviour, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant medicinal products in psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old
Cases of suicidal thoughts and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation (see section 4.8). Physicians should encourage patients to report any distressing thoughts or feelings or depressive symptoms at any time. If while on ARICLAIM therapy, the patient develops agitation or depressive symptoms, specialised medical advice should be sought, as depression is a serious medical condition. If a decision to initiate antidepressant pharmacological therapy is taken, the gradual discontinuation of ARICLAIM is recommended (see Section 4.2).

Use in children and adolescents under 18 years of age
No clinical trials have been conducted with duloxetine in paediatric populations. ARICLAIM should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempts and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger), were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. Long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Medicinal products containing duloxetine
Duloxetine is used under different trademarks in several indications (treatment of diabetic neuropathic pain, major depressive episodes as well as stress urinary incontinence). The use of more than one of these products concomitantly should be avoided.

Hepatitis/increased liver enzymes
Cases of liver injury, including severe elevations of liver enzymes (>10 times upper limit of normal), hepatitis and jaundice have been reported with duloxetine (see section 4.8). Most of them occurred during the first months of treatment. The pattern of liver damage was predominantly hepatocellular. Duloxetine should be used with caution in patients treated with other medicinal products associated with hepatic injury.

Akathisia/psychomotor restlessness
The use of duloxetine has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Sucrose
ARICLAIM gastro-resistant capsules contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Monoamine oxidase inhibitors (MAOIs): due to the risk of serotonin syndrome, ARICLAIM should not be used in combination with nonselective, irreversible monoamine oxidase inhibitors (MAOIs), or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of duloxetine, at least 5 days should be allowed after stopping ARICLAIM before starting an MAOI (see section 4.3).

Serotonin syndrome: in rare cases, serotonin syndrome has been reported in patients using SSRIs (e.g. paroxetine, fluoxetine) concomitantly with serotonergic medicinal products. Caution is advisable if ARICLAIM is used concomitantly with serotonergic antidepressants like SSRIs, tricyclics like clomipramine or amitriptyline, St John's wort (Hypericum perforatum), venlafaxine or triptans, tramadol, pethidine and tryptophan.

CNS medicinal products: caution is advised when ARICLAIM is taken in combination with other centrally acting medicinal products or substances, including alcohol and sedative medicinal products (benzodiazepines, morphinomimetics, antipsychotics, phenobarbital, sedative antihistamines).

Effect of duloxetine on other medicinal products
Medicinal products metabolised by CYP1A2: The pharmacokinetics of theophylline, a CYP1A2 substrate, were not significantly affected by co-administration with duloxetine (60 mg twice daily).
Medicinal products metabolised by CYP2D6: Duloxetine is a moderate inhibitor of CYP2D6. When duloxetine was administered at a dose of 60 mg twice daily with a single dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold. The co-administration of duloxetine (40 mg twice daily) increases steady state AUC of tolterodine (2 mg twice daily) by 71 %, but does not affect the pharmacokinetics of its active 5-hydroxyl metabolite and no dosage adjustment is recommended. Caution is advised if ARICLAIM is co-administered with medicinal products that are predominantly metabolised by CYP2D6 (risperidone, tricyclic antidepressants [TCAs] such as nortriptyline, amitriptyline, and imipramine) particularly if they have a narrow therapeutic index (such as flecainide, propafenone and metoprolol).

Oral contraceptives and other steroidal agents: results of *in vitro* studies demonstrate that duloxetine does not induce the catalytic activity of CYP3A. Specific *in vivo* drug interaction studies have not been performed.

Anticoagulants and antiplatelet agents: Caution should be exercised when duloxetine is combined with oral anticoagulants or antiplatelet agents due to a potential increased risk of bleeding. Furthermore, increases in INR values have been reported when duloxetine was co-administered with warfarin.

Effects of other medicinal products on duloxetine
Antacids and H2 antagonists: co-administration of ARICLAIM with aluminium- and magnesium-containing antacids or with famotidine had no significant effect on the rate or extent of duloxetine absorption after administration of a 40 mg oral dose.

Inhibitors of CYP1A2: because CYP1A2 is involved in duloxetine metabolism, concomitant use of ARICLAIM with potent inhibitors of CYP1A2 is likely to result in higher concentrations of duloxetine. Fluvoxamine (100 mg once daily), a potent inhibitor of CYP1A2, decreased the apparent plasma clearance of duloxetine by about 77% and increased AUC_{0-t} 6-fold. Therefore ARICLAIM should not be administered in combination with potent inhibitors of CYP1A2 like fluvoxamine (see section 4.3).

Inducers of CYP1A2: Population pharmacokinetic studies analyses have shown that smokers have almost 50% lower plasma concentrations of duloxetine compared with non-smokers.

4.6 Pregnancy and lactation

Pregnancy
There are no data on the use of duloxetine in pregnant women. Studies in animals have shown reproductive toxicity at systemic exposure levels (AUC) of duloxetine lower than the maximum clinical exposure (see section 5.3). The potential risk for humans is unknown. Withdrawal symptoms may occur in the neonate after maternal duloxetine use near term. ARICLAIM is contraindicated during pregnancy (see section 4.3).

Breast feeding
Duloxetine is very weakly excreted into human milk based on a study of 6 lactating patients, who did not breast feed their children . The estimated daily infant dose on a mg/kg basis is approximately 0.14% of the maternal dose (see section 5.2). As the safety of duloxetine in infants is not known, the use of ARICLAIM while breast-feeding is not recommended.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. ARICLAIM may be associated with sedation and dizziness. Patients should be instructed that if they experience sedation or dizziness they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects

Stress Urinary Incontinence:

Table 1 gives the adverse reactions observed from spontaneous reporting and in placebo-controlled clinical trials (comprising a total of 7977 patients, 4371 on duloxetine and 3606 on placebo) in SUI and other lower urinary tract disorders.
The most commonly reported adverse events in patients treated with ARICLAIM in clinical trials in SUI and other lower urinary tract disorders were nausea, dry mouthand fatigue -. The data analysis of four 12-week, placebo-controlled clinical trials in patients with SUI, including 958 duloxetine-treated and 955 placebo-treated patients, showed that the onset of the reported adverse events typically occurred in the first week of therapy. However, the majority of the most frequent adverse events were mild to moderate and resolved within 30 days of occurrence (e.g. nausea).

Table 1: Adverse reactions
Frequency estimate: Very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1,000 and <1/100), rare (≥ 1/10,000 and <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Very common	Common	Uncommon	Rare	Very Rare	Frequency not known
Investigations					
		Weight increase Weight decrease Creatinine phosphokinase increase Blood cholesterol increased			
Cardiac Disorders					
	Palpitations	Tachycardia			Supra-ventricular arrhythmia, mainly atrial fibrillation
Nervous System Disorders					
	Headache Dizziness Tremor Nervousness Lethargy	Dysgeusia Disturbance in attention	Myoclonus Dyskinesia		Serotonin syndrome Extrapyramidal symptoms Convulsions

	Somnolence Paraesthesia				Akathisia Psychomotor restlessness
Eye Disorders					
	Blurred vision	Mydriasis Visual disturbance	Glaucoma		
Ear and Labyrinth Disorders					
	Vertigo	Ear pain			
Respiratory, thoracic and mediastinal disorders					
		Yawning	Throat tightness Epistaxis		
Gastrointestinal Disorders					
Nausea (22%) Dry mouth (11.2%)	Constipation Diarrhoea Vomiting Dyspepsia	Eructation Gastroenteritis Stomatitis Halitosis Gastritis Flatulence	Haematochezia		Gastrointestinal haemorrhage
Renals and Urinary Disorders					
		Nocturia Urinary hesitation Urine odour abnormal Dysuria			Urinary retention
Skin and Subcutaneous Tissue Disorders					
	Sweating increased	Night sweats Cold sweat Rash Increased tendency to bruise	Photo-sensitivity reactions		Angioneurotic oedema Stevens-Johnson Syndrome Urticaria
Muscoskeletal and connective tissue disorders					
		Muscle tightness Musculo-skeletal pain Trismus Muscle spasm	Muscle twitching		
Endocrine disorders					
		Hypo-thyroidism			
Metabolism and Nutrition Disorders					
	Appetite decreased	Dehydration	Hyperglycemia (reported especially in diabetic patients)		Hyponatremia, SIADH
Infections and infestations					
		Laryngitis			

Vascular Disorders					
	Hot flush	Flushing Blood pressure increase Syncope[1]	Peripheral coldness Orthostatic hypotension[1] Hypertensive crisis		Hypertension
General Disorders and Administration Site Conditions					
Fatigue (10.3%)	Pruritus Weakness Abdominal pain Chills	Feeling hot Malaise Thirst Feeling abnormal	Feeling cold		Chest pain
Immune system disorders					
		Hyper-sensitivity disorder			Anaphylactic reaction
Hepato-biliary disorders					
		Elevated liver enzymes (ALT, AST, alkaline phosphatase) Hepatitis[2] Acute liver injury			Jaundice Hepatic failure
Reproductive System and Breast Disorders					
		Menopausal symptoms Gynaecological haemorrhage			
Psychiatric Disorders					
	Insomnia Sleep disorder Anxiety Libido decreased Agitation	Bruxism Disorientation Orgasm abnormal Apathy Abnormal dreams			Hallucinations Mania

[1]Cases of orthostatic hypotension and syncope have been reported especially at the initiation of treatment
[2]See section 4.4

Discontinuation of duloxetine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, headache, irritability, diarrhoea, hyperhydrosis and vertigo are the most commonly reported reactions.
Generally, for SSRIs and SNRIs, these events are mild to moderate and self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when duloxetine treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 4.2 and 4.4).

Electrocardiograms were obtained from 755 duloxetine-treated patients with SUI and 779 placebo-treated patients in 12-week clinical trials. The heart rate-corrected QT interval in duloxetine-treated patients did not differ from that seen in placebo-treated patients.

In the 12 week acute phase of three clinical trials of duloxetine in patients with diabetic neuropathic pain, small but statistically significant increases in fasting blood glucose were observed in duloxetine-treated patients . HbA_{1c} was stable in both duloxetine-treated and placebo-treated patients. In the extension phase of these studies, which lasted up to 52 weeks, there was an increase in HbA_{1c} in both the duloxetine and routine care groups, but the mean increase was 0.3% greater in the duloxetine-treated group. There was also a small increase in fasting blood glucose and in total cholesterol in duloxetine-treated patients while those laboratory tests showed a slight decrease in the routine care group.

Diabetic Peripheral Neuropathic Pain
Table 2 gives the adverse reactions observed from spontaneous reporting and in placebo-controlled clinical trials (comprising a total of 4926 patients, 3127 on duloxetine and 1799 on placebo).
The most commonly observed adverse reactions in patients with diabetic neuropathic pain treated with ARICLAIM were: nausea; somnolence, headache and dizziness.

Table 2: Adverse reactions
Frequency estimate: Very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1,000 and <1/100), rare (≥ 1/10,000 and <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Very common	**Common**	**Uncommon**	**Rare**	**Very Rare**	**Frequency not known**
Investigations					
	Weight decrease	Weight increase Creatinine phosphokinase increase	Blood cholesterol increased		
Cardiac Disorders					
	Palpitations	Tachycardia			Supra-ventricular arrhythmia, mainly atrial fibrillation
Nervous System Disorders					
Headache (14.2%)Somnolence (11.1%)	Dizziness Tremor Nervousness Lethargy Paraesthesia	Dysgeusia Disturbance in attention Myoclonus Dyskinesia			Serotonin syndrome Extra-pyramidal symptoms Convulsions Akathisia Psychomotor restlessness
Eye Disorders					
	Blurred vision	Mydriasis Visual disturbance	Glaucoma		
Ear and Labyrinth Disorders					
		Vertigo Ear pain			

Respiratory, thoracic and mediastinal disorders					
	Yawning	Throat tightness Epistaxis			
Gastrointestinal Disorders					
Nausea (21.7%) Dry mouth (13.4%) Diarrhoea (10.2%)	Constipation Vomiting Dyspepsia Flatulence	Eructation Gastroenteritis Stomatitis Gastritis	Halitosis Haematochezia		Gastrointestinal haemorrhage
Renals and Urinary Disorders					
		Nocturia Urinary hesitation Urinary Retention Dysuria			Urine odour abnormal
Skin and Subcutaneous Tissue Disorders					
	Sweating increased Rash	Night sweats Photo-sensitivity reactions Cold sweat Increased tendency to bruise			Angio-neurotic oedema Stevens-Johnson Syndrome Urticaria
Muscoskeletal and connective tissue disorders					
	Musculo-skeletal pain Muscle tightness Muscle spasm	Muscle twitching	Trismus		
Endocrine disorders					
			Hypo-thyroidism		
Metabolism and Nutrition Disorders					
	Decreased Appetite	Hyperglycemia (reported especially in diabetic patients)	Dehydration		Hypo-natremia SIADH
Infections and infestations					
		Laryngitis			
Vascular Disorders					
	Hot flush	Flushing Blood pressure increase Peripheral coldness Orthostatic hypotension[1] Syncope[1]			Hypertension Hypertensive crisis

General Disorders and Administration Site Conditions					
	Fatigue Abdominal pain	Feeling hot Feeling cold Malaise Thirst Feeling abnormal Chills			Chest pain
Immune system disorders					
		Hyper-sensitivity disorder			Anaphylactic reaction
Hepato-biliary disorders					
		Elevated liver enzymes (ALT, AST, alkaline phosphatase) Hepatitis[2] Acute liver injury			Jaundice Hepatic failure
Reproductive System and Breast Disorders					
	Erectile dysfunction	Ejaculation disorder Ejaculation delayed Gynaecological haemorrhage	Menopausal symptoms		
Psychiatric Disorders					
Insomnia (10.2%)	Anxiety Libido decreased Orgasm abnormal Agitation Abnormal dreams	Bruxism Disorientation Sleep disorder Apathy	Mania		Suicidal ideation[3] Suicidal behaviour[3] Hallucinations

[1] Cases of orthostatic hypotension and syncope have been reported especially at the initiation of treatment.
[2] See section 4.4.
[3] Cases of suicidal ideation and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation (see section 4.4).

Discontinuation of duloxetine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, headache, irritability, diarrhoea, hyperhydrosis and vertigo are the most commonly reported reactions.
Generally, for SSRIs and SNRIs, these events are mild to moderate and self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when duloxetine treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 4.2 and 4.4).

In the 12 week acute phase of three clinical trials of duloxetine in patients with diabetic neuropathic pain, small but statistically significant increases in fasting blood glucose were observed in duloxetine-

treated patients. HbA1c was stable in both duloxetine-treated and placebo-treated patients. In the extension phase of these studies, which lasted up to 52 weeks, there was an increase in HbA1c in both the duloxetine and routine care groups, but the mean increase was 0.3% greater in the duloxetine-treated group. There was also a small increase in fasting blood glucose and in total cholesterol in duloxetine-treated patients while those laboratory tests showed a slight decrease in the routine care group.

Electrocardiograms were obtained from 528 duloxetine-treated and 205 placebo-treated patients with diabetic neuropathic pain in clinical trials lasting up to 13-weeks. The heart rate-corrected QT interval in duloxetine-treated patients did not differ from that seen in placebo-treated patients. No clinically significant differences were observed for QT, PR, QRS, or QTcB measurements between duloxetine-treated and placebo-treated patients.

4.9 Overdose

There is limited clinical experience with duloxetine overdose in humans. Cases of overdoses, alone or in combination with other medicinal products, with duloxetine doses of 4800mg were reported. Some fatalities have occurred, primarily with mixed overdoses, but also with duloxetine alone at a dose of approximately 1000 mg. Signs and symptoms of overdose (mostly with mixed medicinal products) included serotonin syndrome, somnolence, vomiting and seizures.

No specific antidote for duloxetine is known but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered.. A free airway should be established. Monitoring of cardiac and vital signs is recommended, along with appropriate symptomatic and supportive measures. Gastric lavage may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal may be useful in limiting absorption. Duloxetine has a large volume of distribution and forced diuresis, haemoperfusion, and exchange perfusion are unlikely to be beneficial.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antidepressants. ATC code: N06AX21

Duloxetine is a combined serotonin (5-HT) and norepinephrine (NE) reuptake inhibitor. It weakly inhibits dopamine reuptake with no significant affinity for histaminergic, dopaminergic, cholinergic and adrenergic receptors.

In animal studies, increased levels of 5-HT and NE in the sacral spinal cord, lead to increased urethral tone via enhanced pudendal nerve stimulation to the urethral striated sphincter muscle only during the storage phase of the micturition cycle. A similar mechanism in women is believed to result in stronger urethral closure during urine storage with physical stress that could explain the efficacy of duloxetine in the treatment of women with SUI.

Duloxetine normalised pain thresholds in several preclinical models of neuropathic and inflammatory pain and attenuated pain behaviour in a model of persistent pain. The pain inhibitory action of duloxetine is believed to be a result of potentiation of descending inhibitory pain pathways within the central nervous system.

Stress Urinary Incontinence:
The efficacy of duloxetine 40 mg given twice daily in the treatment of SUI was established in four double-blind, placebo-controlled studies, that randomised 1913 women (22 to 83 years) with SUI; of these, 958 patients were randomised to duloxetine and 955 to placebo. The primary efficacy measures were Incontinence Episode Frequency (IEF) from diaries and an incontinence specific quality of life questionnaire score (I-QOL).

Incontinence Episode Frequency: in all four studies the duloxetine-treated group had a 50% or greater median decrease in IEF compared with 33% in the placebo-treated group. Differences were observed at each visit after 4 weeks (duloxetine 54%, and placebo 22%), 8 weeks (52% and 29%), and 12 weeks (52% and 33%) of medication.

In an additional study limited to patients with severe SUI, all responses with duloxetine were achieved within 2 weeks.

The efficacy of ARICLAIM has not been evaluated for longer than 3 months in placebo-controlled studies. The clinical benefit of ARICLAIM compared with placebo has not been demonstrated in women with mild SUI, defined in randomised trials as those with IEF < 14 per week. In these women, ARICLAIM may provide no benefit beyond that afforded by more conservative behavioural interventions.

Quality of Life: Incontinence Quality of Life (I-QOL) questionnaire scores were significantly improved in the duloxetine-treated patient group compared with the placebo-treated group (9.2 versus 5.9 score improvement, p<.001). Using a global improvement scale (PGI), significantly more women using duloxetine considered their symptoms of stress incontinence to be improved with treatment compared with women using placebo (64.6% versus 50.1%, p<.001).

ARICLAIM and Prior Continence Surgery: there are limited data that suggest that the benefits of ARICLAIM are not diminished in women with stress urinary incontinence who have previously undergone continence surgery.

ARICLAIM and Pelvic Floor Muscle Training (PFMT): during a 12-week blinded, randomised, controlled study, ARICLAIM demonstrated greater reductions in IEF compared with either placebo treatment or with PFMT alone. Combined therapy (duloxetine + PFMT) showed greater improvement in both pad use and condition-specific quality of life measures than ARICLAIM alone or PFMT alone.

Diabetic Peripheral Neuropathic Pain:
The efficacy of duloxetine as a treatment for diabetic neuropathic pain was established in 2 randomised, 12-week, double-blind, placebo-controlled, fixed dose studies in adults (22 to 88 years) having diabetic neuropathic pain for at least 6 months. Patients meeting diagnostic criteria for major depressive disorder were excluded from these trials. The primary outcome measure was the weekly mean of 24-hour average pain, which was collected in a daily diary by patients on an 11-point Likert scale.

In both studies, duloxetine 60 mg once daily and 60 mg twice daily significantly reduced pain compared with placebo. The effect in some patients was apparent in the first week of treatment. The difference in mean improvement between the two active treatment arms was not significant. At least 30% reported pain reduction was recorded in approximately 65% of duloxetine treated patients versus 40% for placebo. The corresponding figures for at least 50% pain reduction were 50% and 26% respectively. Clinical response rates (50% or greater improvement in pain) were analysed according to whether or not the patient experienced somnolence during treatment. For patients not experiencing somnolence, clinical response was observed in 47% of patients receiving duloxetine and 27% patients on placebo. Clinical response rates in patients experiencing somnolence were 60% on duloxetine and 30% on placebo. Patients not demonstrating a pain reduction of 30% within 60 days of treatment were unlikely to reach this level during further treatment.

Although data from a one-year open label study offer some evidence for longer-term efficacy, no conclusive efficacy data for treatments longer than 12 weeks duration are available from placebo-controlled studies.

5.2 Pharmacokinetic properties

Duloxetine is administered as a single enantiomer. Duloxetine is extensively metabolised by oxidative enzymes (CYP1A2 and the polymorphic CYP2D6), followed by conjugation. The pharmacokinetics of duloxetine demonstrate large intersubject variability (generally 50-60%), partly due to gender, age, smoking status and CYP2D6 metaboliser status.

Duloxetine is well absorbed after oral administration with a C_{max} occurring 6 hours post dose. The absolute oral bioavailability of duloxetine ranged from 32% to 80% (mean of 50%; N=8 subjects). Food delays the time to reach the peak concentration from 6 to 10 hours and it marginally decreases the extent of absorption (approximately 11%).

Duloxetine is approximately 96% bound to human plasma proteins. Duloxetine binds to both albumin and alpha-1 acid glycoprotein. Protein binding is not affected by renal or hepatic impairment.

Duloxetine is extensively metabolised and the metabolites are excreted principally in urine. Both CYP2D6 and CYP1A2 catalyse the formation of the two major metabolites glucuronide conjugate of 4-hydroxy duloxetine and sulphate conjugate of 5-hydroxy,6-methoxy duloxetine. Based upon *in vitro* studies, the circulating metabolites of duloxetine are considered pharmacologically inactive. The pharmacokinetics of duloxetine in patients who are poor metabolisers with respect to CYP2D6 has not been specifically investigated. Limited data suggest that the plasma levels of duloxetine are higher in these patients.

The elimination half-life of duloxetine after an oral dose ranges from 8 to 17 hours (mean of 12 hours). After an intravenous dose the plasma clearance of duloxetine ranges from 22 l/hr to 46 l/hr (mean of 36 l/hr) After an oral dose the apparent plasma clearance of duloxetine ranges from 33 to 261 l/hr (mean 101 l/hr).

Special populations:
Gender: pharmacokinetic differences have been identified between males and females (apparent plasma clearance is approximatively 50% lower in females). Based upon the overlap in the range of clearance, gender-based pharmacokinetic differences do not justify the recommendation for using a lower dose for female patients.

Age: pharmacokinetic differences have been identified between younger and elderly females (≥65 years) (AUC increases by about 25% and half-life is about 25% longer in the elderly), although the magnitude of these changes is not sufficient to justify adjustments to the dose. As a general recommendation, caution should be exercised when treating the elderly (see sections 4.2 and 4.4).

Renal impairment: end stage renal disease (ESRD) patients receiving dialysis had a 2-fold higher duloxetine C_{max} and AUC values compared to healthy subjects. Pharmacokinetic data on duloxetine is limited in patients with mild or moderate renal impairment.

Hepatic insufficiency: moderate liver disease (Child Pugh Class B) affected the pharmacokinetics of duloxetine. Compared with healthy subjects, the apparent plasma clearance of duloxetine was 79% lower, the apparent terminal half-life was 2.3 times longer, and the AUC was 3.7 times higher in patients with moderate liver disease. The pharmacokinetics of duloxetine and its metabolites have not been studied in patients with mild or severe hepatic insufficiency.

Nursing mothers: The disposition of duloxetine was studied in 6 lactating women who were at least 12-weeks postpartum. Duloxetine is detected in breast milk, and steady-state concentrations in breast milk are about one-fourth those in plasma. The amount of duloxetine in breast milk is approximately 7 μg/day while on 40 mg twice daily dosing. Lactation did not influence duloxetine pharmacokinetics.

5.3 Preclinical safety data

Duloxetine was not genotoxic in a standard battery of tests and was not carcinogenic in rats.

Multinucleated cells were seen in the liver in the absence of other histopathological changes in the rat carcinogenicity study. The underlying mechanism and the clinical relevance are unknown.

Female mice receiving duloxetine for 2 years had an increased incidence of hepatocellular adenomas and carcinomas at the high dose only (144 mg/kg/day), but these were considered to be secondary to hepatic microsomal enzyme induction. The relevance of this mouse data to humans is unknown. Female rats receiving duloxetine before and during mating and early pregnancy had a decrease in maternal food consumption and body weight, oestrous cycle disruption, decreased live birth indices and progeny survival, and progeny growth retardation at systemic exposure levels estimated to be at the most at maximum clinical exposure (AUC). In an embryotoxicity study in the rabbit, a higher incidence of cardiovascular and skeletal malformations was observed at systemic exposure levels below the maximun clinical exposure (AUC). No malformations were observed in another study testing a higher dose of a different salt of duloxetine. In pre/postnatal toxicity study in the rat, duloxetine induced adverse behavioural effects in the offspring at systemic exposures levels below maximum clinical exposure (AUC).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Hypromellose.
Hydroxypropyl methylcellulose acetate succinate
Sucrose
Sugar spheres
Talc
Titanium dioxide (E171)
Triethyl citrate.

Capsule shell:
Gelatin
Sodium Lauryl Sulfate
Titanium Dioxide (E171)
Indigo Carmine (E132)
Edible Black Ink.

Edible Ink:
Black Iron Oxide-Synthetic (E172)
Propylene glycol
Shellac

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture. Do not store above 30°C.

6.5 Nature and contents of container

Polyvinylchloride (PVC), Polyethylene (PE), and Polychlorotrifluoroethylene (PCTFE) blister sealed with an aluminum foil.

Packs of 28 and 56 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland BV, Grootslag 1-5, NL-3991 RA Houten, The Netherlands.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/283/001
EU/1/04/283/007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11 August 2004

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Lilly S.A.
Avda. de la Industria Nº 30,
28108 Alcobendas
Madrid
Spain

B CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OTHER CONDITIONS**

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTONS FOR 40 MG HARD GASTRO-RESISTANT CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

ARICLAIM 40 mg, hard gastro-resistant capsules.
Duloxetine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 40 mg duloxetine (as hydrochloride)

3. LIST OF EXCIPIENTS

Contains sucrose
See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

28 hard gastro-resistant capsules
56 hard gastro-resistant capsules
98 hard gastro-resistant capsules
140 hard gastro-resistant capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}.

9. SPECIAL STORAGE CONDITIONS

Store in the original package. Do not store above 30 °C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland BV, Grootslag 1-5, NL-3991 RA, Houten, The Netherlands.

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/283/002-005

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ARICLAIM 40 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR 98 CAPSULES (40 MG) AS INTERMEDIATE PACK / COMPONENT OF A MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

ARICLAIM 40 mg hard gastro-resistant capsules
Duloxetine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 40 mg duloxetine (as hydrochloride).

3. LIST OF EXCIPIENTS

Contains sucrose.
See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

98 capsules
Component of a multipack comprising 2 packs, each containing 98 capsules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Store in the original package. Do not store above 30 °C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland BV, Grootslag 1-5, NL-3991 RA, Houten, The Netherlands.

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/283/004

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ARICLAIM 40 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER WRAPPER LABEL ON MULTIPACKS (2X98 CAPSULES, 40 MG) WRAPPED IN FOIL (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

ARICLAIM 40 mg hard gastro-resistant capsules
Duloxetine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 40 mg duloxetine (as hydrochloride).

3. LIST OF EXCIPIENTS

Contains sucrose
See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack comprising 2 packs, each containing 98 capsules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Store in the original package. Do not store above 30 °C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland BV, Grootslag 1-5, NL-3991 RA, Houten, The Netherlands.

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/283/006

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ARICLAIM 40 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS (40 mg hard gastro-resistant capsules)

1. NAME OF THE MEDICINAL PRODUCT

ARICLAIM 40 mg hard gastro-resistant capsules
Duloxetine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Lilly

3. EXPIRY DATE

<EXP {MM/YYYY}.

4. BATCH NUMBER

Lot:

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTONS FOR 20 MG HARD GASTRO-RESISTANT CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

ARICLAIM 20 mg hard gastro-resistant capsules
Duloxetine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 20 mg duloxetine (as hydrochloride).

3. LIST OF EXCIPIENTS

Contains sucrose.
See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

28 hard gastro-resistant capsules
56 hard gastro-resistant capsules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}.

9. SPECIAL STORAGE CONDITIONS

Store in the original package. Do not store above 30 °C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland BV, Grootslag 1-5, NL-3991 RA, Houten, The Netherlands.

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/283/001
EU/1/04/283/007

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ARICLAIM 20 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS (20 mg hard gastro-resistant capsules)

1. NAME OF THE MEDICINAL PRODUCT

ARICLAIM 20 mg hard gastro-resistant capsules
Duloxetine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Lilly

3. EXPIRY DATE

<EXP {MM/YYYY}.

4. BATCH NUMBER

Lot:

5. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

ARICLAIM 40 mg hard gastro -resistant capsules
ARICLAIM 20 mg hard gastro -resistant capsules
Duloxetine (as hydrochloride)

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to
- others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What ARICLAIM is and what it is used for
2. Before you take ARICLAIM
3. How to take ARICLAIM
4. Possible side effects
5. How to store ARICLAIM
6. Further information

1. WHAT ARICLAIM IS AND WHAT IT IS USED FOR

ARICLAIM increases the levels of serotonin and norepinephrine in the nervous system.
ARICLAIM is a medicine to be taken by mouth to treat Stress Urinary Incontinence (SUI) in women or to treat a condition called diabetic neuropathic pain in adults.

Stress urinary incontinence is a medical condition in which patients have accidental loss or leakage of urine during physical exertion or activities such as laughing, coughing, sneezing, lifting, or exercise.

ARICLAIM is believed to work by increasing the strength of the muscle that holds back urine when you laugh, sneeze, or perform physical activities.

The efficacy of ARICLAIM is reinforced when combined with a training program called Pelvic Floor Muscle Training (PFMT).

Neuropathic pain is a medical condition in which the pain is commonly described as burning, stabbing, stinging, shooting or aching or like an electric shock. There may be loss of feeling in the affected area, or sensations such as touch, heat, cold or pressure may cause pain.

The effect of ARICLAIM may be noticeable in many patients with diabetic neuropathic pain within 1 week of treatment.

2. BEFORE YOU TAKE ARICLAIM

Do not take ARICLAIM
- If you are allergic (hypersensitive) to duloxetine or any of the inactive ingredients of ARICLAIM.
- If you are taking or have taken within the last 14 days, another medicine known as a monoamine oxidase inhibitor - MAOI (see section below ‘Taking other medicines’).
- If you have liver disease.
- If you are pregnant or breast-feeding.

- If you are taking fluvoxamine which is usually used to treat depression, ciprofloxacin or enoxacine which are used to treat some infections.
- If you have severe kidney disease.
- If you suffer from uncontrolled high blood pressure.

Take special care with ARICLAIM
The following are reasons why ARICLAIM may not be suitable for you. If any of them apply to you, talk to your doctor before you take the medicine:

- You are taking other medicines to treat depression.
- You are taking a herbal treatment containing St. John's Wort (Hypericum perforatum).
- You have kidney disease.
- You have had seizures (fits).
- You suffer from or have suffered from mania or bipolar disorder.
- You have eye problems, such as certain kinds of glaucoma (increased pressure in the eye).
- You have a history of bleeding disorders (tendency to develop bruises).
- You are at risk of low sodium levels.
- You have high blood pressure.
- You are currently being treated with another medicine which may cause liver damage.
- You are taking other medicines containing duloxetine.
- You have intolerance to some sugars (see below).
- You are considering stopping ARICLAIM (see section 3).

ARICLAIM may cause a sensation of restlessness or an inability to sit or stand still. You should tell your doctor if this happens to you.

Although ARICLAIM is not indicated for the treatment of depression, its active ingredient (duloxetine) also exists as an antidepressant medication. Suicidal thoughts and behaviours have been reported during duloxetine therapy or early after treatment discontinuation. Whilst depression and other serious mental illnesses themselves are the most important causes of suicidal thoughts and actions, the risk of such symptoms might be higher in patients who have previously had thoughts of self harm and in young adult patients. Tell your doctor immediately if you have any distressing thoughts or feelings at any time or if you are feeling changes in mood like sadness, apathy or agitation, or if you start treatment for depression.

Use in children and adolescents under 18 years of age
ARICLAIM should not be used for children and adolescents under the age of 18 years. Also, you should know that patients under 18 have an increased risk of side-effects such as suicide attempt, suicidal thoughts and hostility (predominantly aggression, oppositional behaviour and anger) when they take this class of medicines. Also, the long-term safety effects concerning growth, maturation, and cognitive and behavioural development of ARICLAIM in this age group have not yet been demonstrated.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. The main ingredient of ARICLAIM, duloxetine, is used in other medicines for other conditions (depression and urinary incontinence). Using more than one of these medicines at the same time should be avoided. Check with your doctor if you are already taking other medicines containing duloxetine.

Your doctor should decide whether you can take ARICLAIM with other medicines. Do not start or stop taking any medicines, including those bought without a prescription and herbal remedies, before checking with your doctor.

Monoamine Oxidase Inhibitors (MAOI): you should not take ARICLAIM with an MAOI or within 14 days of stopping an MAOI. Taking an MAOI together with many prescription medicines, including ARICLAIM, can cause serious or even life-threatening side effects. You must wait at least 14 days

after you have stopped taking an MAOI before you can take ARICLAIM. Also, you need to wait at least 5 days after you stop taking ARICLAIM before you take an MAOI.

CNS medicines: caution is advised when ARICLAIM is taken in combination with other centrally acting medicines or substances, including alcohol and sedative medicines(benzodiazepines, morphinomimetics, antipsychotics, phenobarbital, sedative antihistamines).
Inform your doctor if you are taking any of these medicines.

Serotonin syndrome: you should tell your doctor if you are taking any of the medicines that act in a similar way to duloxetine. Examples of these medicines include: triptans, tramadol, tryptophan, certain antidepressants: SSRIs (such as paroxetine and fluoxetine), tricyclics (such as clomipramine, amitriptyline) and venlafaxine. These medicines increase the risk of side effects; if you get any unusual symptom taking any of these medicines together with ARICLAIM, you should see your doctor.

Oral -anticoagulants: You should tell you doctor if you are taking oral –anticoagulants (medicines which thin the blood). These medicines might increase the risk of bleeding.

Taking ARICLAIM with food and drink
ARICLAIM may be taken with or without food. You should take extra care if you drink alcohol while taking ARICLAIM.

Pregnancy and breast-feeding
ARICLAIM should not be used during pregnancy and if you are breast feeding. Tell your doctor if you become pregnant, or you are trying to become pregnant, while you are taking ARICLAIM.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
ARICLAIM may make you feel sleepy of dizzy. Do not drive or use any tools or machines until you know how ARICLAIM affects you.

Important information about some of the ingredients of ARICLAIM
ARICLAIM contains sucrose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE ARICLAIM

Always take ARICLAIM exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The recommended dose of ARICLAIM for the treatment of Stress Urinary Incontinence is 40 mg twice a day (in the morning and late afternoon/evening). Your doctor may decide to start your treatment with one capsule of 20 mg twice a day for two weeks before increasing the dose to 40 mg twice a day.
The usual dose of ARICLAIM for the treatment Neuropathic pain is 60 mg once a day, but your doctor will prescribe the dose that is right for you.

ARICLAIM is for oral use. You should swallow your capsule whole with a drink of water.

To help you remember to take ARICLAIM, you may find it easier to take it at the same times every day.

Do not stop taking ARICLAIM without talking to your doctor.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

If you take more ARICLAIM than you should
Call your doctor or pharmacist immediately if you take more than the amount of ARICLAIM prescribed by your doctor.

If you forget to take ARICLAIM
Do not take a double dose to make up for forgotten doses.

If you miss a dose, take it as soon as you remember. However, if it is time for your next dose, skip the missed dose and take only a single dose as usual. Do not take more than the daily amount of ARICLAIM that has been prescribed for you in one day.

If you stop taking ARICLAIM
Do not stop taking your capsules without the advice of your doctor even if you feel better. If your doctor thinks that you no longer need ARICLAIM he will ask you to reduce your dose over 2 weeks. Some patients, who suddenly stop taking ARICLAIM after more than 1 week of therapy, have had symptoms such as dizziness, tingling feelings like pins and needles, sleep disturbances (vivid dreams, nightmares, inability to sleep), feeling restless or agitated, feeling anxious, feeling sick (nausea) or being sick (vomiting), tremor (shakiness), headaches, feeling irritable, diarrhoea, excessive sweating or vertigo. . These symptoms are usually not serious and disappear within a few days, but if you have symptoms that are troublesome you should ask your doctor for advice.

4. POSSIBLE SIDE EFFECTS

Like all medicines, ARICLAIM can cause side effects, although not everybody gets them. These effects are normally mild to moderate and often disappear after a short time.

Very common side effects (these can affect more than 10 in 100 patients treated) with ARICLAIM when taken to treat stress urinary incontinence
Feeling sick (nausea), dry mouth, and tiredness.

Very common side effects (these can affect more than 10 in 100 patients treated) with ARICLAIM when taken to treat diabetic neuropathic pain
Feeling sick (nausea), somnolence, headache and dizziness.

Common side effects (these can affect more than 1 in 100 patients treated)
- Anxiety, feeling agitated or having abnormal dreams.
- Dizziness, tremor or numbness, including numbness or tingling of the skin.
- Constipation, being sick (vomiting), heartburn or breaking wind, weight loss or lack of appetite.
- Blurred eyesight.
- Feeling the heart pumping in the chest or hot flushes.
- Problems getting an erection, changes in orgasm or less sex drive.
- (itchy) Rash.
- Muscle pain, muscle tightness or muscle spasm.

Uncommon side effects (these can affect less than 1 in 100 patients treated)
- Throat inflammation.
- Feeling disorientated, feeling sleepy lack of motivation or increased yawning.
- Tasting things differently than usual, disturbance in attention or spasms and involuntary movements of the muscles.
- Weight increase, burping, indigestion or gastroenteritis.
- Inflammation of the liver that may cause abdominal pain, tiredness or yellow coloration of the skin.
- Vertigo and ear pain.
- Larger pupils (the dark centre of the eye) or visual disturbance.

- Flushing, increase in blood pressure, feeling cold in your fingers and/or toes, feeling dizzy (particularly when standing up too quickly), fast or irregular heart beat, night sweats, cold sweats, shivering or fainting.
- Changes in ejaculation, abnormal periods, including heavy or prolonged periods
- Allergic reactions, increased tendency to bruise, blisters or sensitivity to sunlight.
- Muscle twitching.
- Need to pass urine during the night or difficulty or inability to pass urine.
- Grinding of teeth, dehydration, feeling hot/cold, thirst, throat tightness or nose bleeds

Rare side effects (these can affect less than 1 in 1,000 patients treated)
- Mania (a disorder which symptoms are over activity, racing thoughts and decrease need for sleep)
- Increased level of sugar in the blood or bad breath.
- Increased pressure in the eye.
- Menopausal symptoms.
- Contraction of the jaw muscle.
- Decrease of activity of the thyroid gland, chest or stomach pain.

Other possible side effects
- Experiencing hallucinations, suicidal thoughts or behaviour.
- A sensation of restlessness or an inability to sit or stand still, "Serotonin syndrome" (a rare reaction which may cause feelings of great happiness, drowsiness, clumsiness, restlessness, feeling of being drunk, fever, sweating or rigid muscles), fits or stiffness.
- Passing bright red blood in your stools vomiting blood, or black tarry stools (faeces).
- Abnormal urine odour.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE ARICLAIM

Keep out of the reach and sight of children

Do not use ARICLAIM after the expiry date which is stated on the carton.

Store in the original pack. Do not store above 30 °C.

6. FURTHER INFORMATION

What ARICLAIM contains
The active substance is duloxetine. Each capsule contains 20 or 40 mg of duloxetine (as hydrochloride).

The other ingredients are:
Capsule content: hypromellose, hydroxypropyl methylcellulose acetate succinate, sucrose, sugar spheres, talc, titanium dioxide (E171), triethyl citrate.
Capsule shell: gelatin, sodium lauryl sulphate, titanium dioxide (E171), indigo carmine (E132), iron oxide red and iron oxide yellow, edible black ink.
Edible Ink: Black Iron Oxide-Synthetic (E172), Propylene glycol, Shellac.

What ARICLAIM looks like and contents of the pack
ARICLAIM is a hard gastro-resistant capsule.

Each capsule of ARICLAIM contains pellets of the active substance with a covering to protect them from stomach acid.

ARICLAIM is available in 2 strengths: 20 and 40 mg.
The 40 mg capsule has an opaque orange body imprinted with ’40 mg’ and an opaque blue cap, imprinted with ‘9545’.
The 20 mg capsule has an opaque blue body imprinted with ’20 mg’ and an opaque blue cap, imprinted with ‘9544’.

ARICLAIM 40 mg is available in blister packs of 28, 56, 98, 140 and 196 (2 x 98) capsules.
ARICLAIM 20 mg is available in blister packs of 28 and 56 capsules.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder: Marketing Authorisation Holder: Eli Lilly Nederland BV, Grootslag 1-5, NL-3991 RA Houten, The Netherlands.
Manufacturer: Lilly S.A., Avda. De la Industria, 30, 28108 Alcobendas, Madrid, Spain.

For any information about this medicine product, please contact the local representative of the Marketing Authorisation Holder.

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Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu.